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protein, one copy of said gene being operationally linked to one of said two or more inserted DNA sequences, said DNA sequence being expressed as a polypeptide of a fusion protein comprising said heteromeric receptor on the surface of said filamentous bacteriophage or as a soluble polypeptide.

REMARKS

Claims 1-5, 7, 8, 16-33 and 66-77 are pending. By the present communication claims 66 and 71 have been amended. Support for the amendments to the claims can be found in the specification including, for example, on page 5, lines 14-23; page 7, lines 1-17 and page 8, lines 17-31. Accordingly, the amendments do not introduce new matter and entry thereof is respectfully requested. A marked up version of the amended claims is provided in Appendix A, attached hereto.

In regard to the informalities in the drawings, Applicant is preparing and will submit formal drawings similar to those published in U.S. Pat No. 6,027,933 in a separate paper. Applicant respectfully requests that amendments changing the recited subparts of the figures to capital letters be deferred until that time, as the number of subparts for several of the figures will likely change.

Rejections under 35 U.S.C. § 112, first paragraph

Claims 1-5, 7, and 77 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement because the

specification does not adequately describe a method by which a heteromeric receptor is expressed on the surface of a cell. The Office Action relies on Wilson et al. in asserting that the gene VIII protein product is expressed on the inner membrane of a cell. The Office Action alleges that expression of a gene VIII fused heteromeric receptor on the inner membrane of a procaryotic cell is not expression on the surface of the cell. The Office Action further alleges that the gene VIII protein product is not anchored to the cell surface via filamentous phage.

In response to the assertion in the Office Action mailed October 22, 1999, that the specification does not enable expression of gVIII fusion products on the surface of a cell, Applicant provided, in the response mailed April 24, 2000, multiple examples of guidance in the specification that would have enabled one skilled in the art to make and use heteromeric receptors as gVIII fusion products expressed on the surface of a cell. Applicant further provided two references as exhibits that demonstrated that the methods taught in the specification would have been known to result in expression of a heteromeric receptor on the surface of a cell. The Examiner has not identified any deficiency in the guidance provided in the specification. Rather, the Examiner has alleged that the exhibits do not describe surface expression of the gVIII protein product allegedly because the gVIII product is expressed on the inner membrane of a host cell.

As Applicant has previously contended, the specification sufficiently enables the claimed functional gene

VIII-heteromeric receptor fusion product expressed on the surface of a procaryotic cell. One skilled in the art would have known that the surface of a procaryotic cell includes a variety of layers including, for example, the inner membrane and outer membrane which are separated by a peptidoglycan wall and periplasmic space. Therefore, methods for exporting a heteromeric receptor from the cytosol to any of these layers would have been known by one skilled in the art to result in surface expression of the heteromeric receptor. Accordingly, guidance provided in the specification including, for example, methods taught for expression of a heteromeric receptor at the inner membrane would have been known to yield a surface expressed heteromeric receptor.

Moreover, as Applicant has previously contended, receptor proteins expressed on the inner membrane layer of a procaryotic cell surface were known, at the time of filing, to be cell surface receptors. Further evidence corroborating the teachings in the specification and Applicant's contentions can be found described on pages 759-760 of Alberts et al., Molecular Biology of the Cell Garland, New York (1983), attached as Exhibit A. Alberts et al. describes four classes of mutants involved in chemotaxis including "cell surface receptors" as stated on page 759, lines 9-11. Alberts et al. identifies the methyl accepting chemotaxis proteins (MCPs) as cell surface receptors of the chemotaxis signal transduction system on page 759, lines 24-31, where the MCPs are described as "cell surface receptors" that fail to detect certain chemical signals. As described in the legend to figure 13-48, on page 760, the MCP acts as both a

receptor and transducer and as shown in figure 13-48, is localized to the inner membrane of the procaryotic cell. Therefore, at the time the application was filed, one skilled in the art would have known that a receptor expressed at the inner membrane of a procaryotic cell is expressed on the surface of the cell.

In the Response mailed April 24, 2000, Applicant submitted Marvin and Wachtel as Exhibit A and pointed out that Figure 1 shows coat proteins, including the gVIII product, anchored on the cell surface via membrane anchoring as well as via the attached phage particle. Applicant contends that the Examiner's assertion that one skilled in the art would not have equivocated expression on the surface of a virus, in the arrangement shown in the figure, as expression on the surface of the cell is unfounded. Specifically, neither Marvin and Wachtel nor any of the other references of record refute that a phage particle extruding through the cell as shown in the figure is on the surface of a cell. Furthermore, one skilled in the art would have known that a phage particle can be on the surface even if it is being extruded because it is impossible to extrude a particle from the interior of a cell to the extracellular milieu without the particle, at some point, being on the surface of the cell.

Accordingly, Applicant respectfully requests that rejection of claims 1-5, 7, and 77, under 35 U.S.C. § 112, first paragraph be withdrawn.

Claims 1-4, 7, 16-19, 21-29, 31, 32, 66-75, and 77 stand rejected under 35 U.S.C. § 112, first paragraph, allegedly because the disclosure does not enable expression of functional portions of any heteromeric receptor proteins, other than the variable heavy and variable light chains of immunoglobulins, on the surface of filamentous bacteriophage. The Office Action appears to rely on the description of ligand gated ion channels in Nakanishi in alleging that one skilled in the art would not have accepted description in the specification as applicable to all receptor proteins. The Office Action further alleges that one would not accept that a receptor which functions as a pentameric complex within a cellular membrane could be functionally expressed on the surface of a bacteriophage.

Applicant contends that arguments to the rejection mailed October 22, 1999, have been submitted in the response mailed April 24, 2000, but have not been adequately addressed by the Examiner. For example, Applicant has identified teaching and guidance in the specification which provides methods for making and using antibodies and other receptors of the claimed invention. Applicant has further argued that the methods exemplified in the specification with antibodies would have been recognized by one skilled in the art as applicable to other receptors because antibodies were known in the art to be receptors. Specifically, Applicant supported the assertion that antibodies would have been recognized as receptors by pointing out teachings in the specification that antibodies are heteromeric receptors. In this regard, Applicant has consistently set forth that the specification defines

"heteromeric receptors," on page 5, lines 14-23, as proteins composed of two or more subunits which together exhibit binding activity toward a particular molecule and explicitly includes antibodies, and fragments thereof. Moreover, Applicant has provided extrinsic evidence in the form of a definition of the term receptor that included antibodies in the term. Citation of a reference describing a specific class of receptors and alleging that antibodies are not art recognized receptors does not negate the teachings in the specification and the fact that those skilled in the art have recognized antibodies as receptors.

Further, Applicant submits that Applicant may be his or her own lexicographer as long as the meaning assigned to the term is not repugnant to the term's well known usage. In re Hill, 161 F.2d 367, 73 USPQ 482 (CCPA 1947).

Applicant respectfully submits that inclusion of antibodies, and fragments thereof, in the term "heteromeric receptor" is not repugnant to the term's well known usage. Applicant has provided extrinsic evidence supporting that antibodies were known in the art as heteromeric receptors. As has been well-established by the courts, an Examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention (*In re Wright,* 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). For example, in regard to the Examiner's burden, the courts have indicated that:

> As a matter of Patent Office practice, then, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. Marzocchi 439 F.2d 220, 223 (CCPA, 1971).

In its decision the court then goes on to say:

> it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement.

Marzocchi 439 F.2d 220, 224 (CCPA, 1971). Applicant contends that the Examiner has not established non-enablement because the Examiner has not supported his assertion that antibodies are not receptors with acceptable evidence or reasoning. Nor has the Examiner provided a basis as to why antibodies, regardless of what terminology is used to refer to them, would not be sufficient to enable one skilled in the art to practice the

claimed invention with other heteromeric receptors given the teachings and guidance in the specification.

Applicant contends that inclusion of antibodies, and fragments thereof, as heteromeric receptors is consistent with the definitions of record. For example, Applicant has provided in the response mailed April 24, 2000, a definition of the term receptor which clearly includes antibodies as receptors. The Office Action has not indicated any contradiction between this definition and that provided in the specification.

The Office Action alleges that Webster's Collegiate Dictionary defines the term "receptor" as "a chemical group or molecule (as a protein) on the cell surface or in the cell interior that has an affinity for a specific chemical group, molecule or virus." Applicant respectfully submits that in view of the guidance provided in the specification and that which was known in the art one skilled in the art would have known that the antibodies described in the specification are consistent with this definition. Specifically, one skilled in the art would have known that an antibody, or fragment thereof, constitutes "a chemical group or molecule (as a protein);" an antibody, or fragment thereof, can be expressed "on the cell surface" as is the case for Igm and other antibodies, for examples. Moreover, one skilled in the art would have known that an antibody or fragment thereof "has affinity for a specific chemical group, molecule or virus," all of which are known to be forms of antigens. Therefore, recombinant antibodies including, for example, those taught in the specification would have been

accepted by one skilled in the art to be receptors according to the definition cited in the Office Action.

Moreover, none of the art of record supports the alleged exclusion of antibodies, or fragments thereof, from being encompassed by the term heteromeric receptor. For example, Nakanishi, Science 258:597-603 (1992) does not support the alleged exclusion of antibodies from being receptors. Nakanishi describes glutamate receptors and classification schemes for the family of glutamate receptors. Nakanishi also compares glutamate receptors to a broader class of receptors identified as ligand gated ion channels. However, Nakanishi does not describe a number of well known receptors including, for example, G protein receptors, integrins, growth factor receptors/tyrosine kinases, or immunoglobulins. Thus, one skilled in the art would not have understood antibodies to be excluded from the broader class including all receptors because Nakanishi makes no attempt to classify all receptors. Furthermore, there is no indication in Nakanishi that antibodies or any of the above recited receptors are excluded from being identified as receptors. Therefore, Nakanishi does not support the Office Action's alleged exclusion of antibodies from being receptors.

Based on the inclusion of antibodies as heteromeric receptors in the definition provided in the specification and the inclusion of antibodies as receptors according to all of the definitions of "receptor" that are of record, Applicant concludes that an antibody would have been well known to one skilled in the art to be a heteromeric receptor. Therefore, the specification

sufficiently enables the full scope of the claims reciting functional heteromeric receptors because methods exemplified in the specification with antibodies would have been recognized by one skilled in the art as applicable to other heteromeric receptors.

In regard to transmitter receptors, Applicant respectfully submits that the claims recite functional heteromeric receptors expressed on the surface of a procaryotic cell or filamentous bacteriophage. As set forth previously, Applicant does not claim all forms of heteromeric receptors. Instead, the claims are directed to only those first and second polypeptides which form functional heteromeric receptors. Thus, the claims do not encompass an integral membrane polypeptide expressed on the surface of a filamentous phage if they would not assemble to a functional heteromeric receptor as described and claimed. In this regard, Applicant has set forth and the specification teaches how to make and use the claimed invention with a variety of heteromeric receptors, having known coding sequences or coding sequences which can be determined, using routine methods taught in the specification or known in the art.

Accordingly, Applicant respectfully requests that rejection of claims 1-4, 7, 16-19, 21-29, 31, 32, 66-75, and 77 under 35 U.S.C. § 112, first paragraph, be withdrawn.

Rejections under 35 U.S.C. § 112, second paragraph

Claims 70 and 75 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly vague and indefinite. Claims 70 and 75 are rejected as vague and indefinite allegedly because the criteria for determining at what point similar sequences cease to be substantially the same is unclear.

Applicant respectfully traverses the rejection and maintains that claims 70 and 75 are sufficiently clear to allow one skilled in the art to determine the metes and bounds of the claims. Applicant has previously pointed out that one skilled in the art would have been capable of identifying one sequence as being substantially the same as another sequence based upon, for example, direct comparison of sequences and comparison of the function of the sequences in the recited vector. Further to previous arguments, Applicant submits that a sequence substantially similar to SEQ ID NOS:1 or 5, in addition to having similar sequence, would retain the functions of the elements claimed by the sequence and taught in the specification. For example, the claimed vector contains a wild type M13 gVIII and a psuedo-wild type gVIII in addition to cloning sites and sequences necessary for expression such as a promoter, signal sequence and translation initiation signals.

Moreover, the specification teaches that minor changes can be made in a vector to yield substantially the same sequence. For example, page 23, line 28, through page 24, line 18, teaches a number of mutations that create restriction sites in the

vectors without altering the amino acid sequence of the encoded product. Further examples of mutations that yield substantially similar vectors are provided on page 26, lines 6-15, which teaches that a deleted codon can be tolerated if it does not affect function of the encoded polypeptide. Therefore, one skilled in the art would have known from the teachings and guidance provided in the specification that vectors containing minor sequence variations that do not alter the function of the claimed vector are substantially the same vector.

Accordingly, Applicant requests that rejections under 35 U.S.C. § 112, second paragraph be withdrawn.

Rejections under 35 U.S.C. § 103

Claims 66-75 stand rejected under 35 U.S.C. § 103 as allegedly obvious over Huse et al. (Science 246:1275-1281, 1989), in view of Ladner et al. (WO 88/06630, 1988) and U.S. Pat. No. 5,223,409 (Ladner et al.). The Office Action alleges that U.S. Pat. No. 5,223,409 demonstrates that the express limitations of claims 66-75 are suggested by the cited art. In this regard, the Office Action alleges that the recited elements "capable of being operationally linked to a DNA sequence encoding a polypeptide of a heteromeric receptor" and "necessary for the coexpression of two or more inserted DNA sequences encoding polypepetides which form heteromeric receptors" are not distinguishing over U.S. Pat. No. 5,223,409 because they are functional statements.

Applicant respectfully traverses the rejection and maintains that the claimed vectors would not have been obvious over Huse et al. in light of Ladner et al. and U.S. Pat. No. 5,223,409 for the reasons of record. Nevertheless, in order to further prosecution, Applicant has amended claims 66 and 71 to recite a DNA sequence being expressed as a polypeptide of a fusion protein comprising the heteromeric receptor on the surface of the filamentous bacteriophage or as a soluble polypeptide.

Applicant maintains previous arguments that the claimed vectors are not obvious over Huse et al. in view of Ladner et al. and U.S. Patent No. 5,223,409 because the references taken alone or in combination do not teach or suggest a vector with the dual capabilities of the claimed vectors. Claims 66-71, as amended, are directed to a vector that expresses a polypeptide of a fusion protein including a heteromeric receptor either on the surface of a filamentous bacteriophage coat protein or as a soluble polypeptide. Applicant contends that U.S. Patent No. 5,223,409 does not teach or suggest a vector which expresses a polypeptide of a fusion protein comprising a heteromeric receptor much less in either soluble or surface bound form. Furthermore, such a vector is not taught or suggested in Huse et al. or the Ladner et al. publication. Absent such a teaching or suggestion, Applicant contends that the amended claims would not have been obvious.

Furthermore, Applicant maintains that the claimed vectors would not have been obvious over Huse et al. in view of Ladner et al. and U.S. Patent No. 5,223,409 because the references taken alone or in combination would not have provided

a reasonable expectation of success that a functional heteromeric receptor would self assemble on the surface of a procaryotic cell. Applicant maintains that one skilled in the art would not have been motivated to make and use the claimed vectors encoding a polypeptide of a fusion protein comprising a heteromeric receptor absent a reasonable expectation of success that the expressed polypeptide would undergo a bi-molecular association event following anchoring into the membrane, as a filamentous bacteriophage coat protein fusion protein. Therefore, the vector recited in claims 66-70 as encoding a polypeptide expressed as a fusion protein comprising a heteromeric receptor and the vector recited in claims 71-75 as having sequences necessary for the expression of two or more polypeptides encoding a surface-expressed fusion protein comprising a heteromeric receptor would not have been obvious. Accordingly, withdrawl of the rejection of claims 66-75, under 35 U.S.C. § 103, is respectfully requested.

Double-patenting rejections

Claims 16-32 and 68-75 stand provisionally rejected under 35 U.S.C. § 101 as claiming the same invention as that of claims 1-33 and 68-75 of application serial number 08/470,297, now patent number 6,027,933.

Applicant respectfully traverses the rejection because claims 16-32 and 68-75 do not claim the same invention claimed in application serial number 08/470,297, now patent number 6,027,933. Claims 1-8, 16-33, and 68-75, of application serial

number 08/470,297, were previously cancelled. Claims 9-15 have been allowed in patent number 6,027,933 as claims 1-7 respectively. Applicant respectfully submits that claims 16-25 and 26-33 of the application are directed to a cloning system or plurality of vectors and specifically recite vectors having diverse populations of DNA sequences encoding polypeptides of a heteromeric receptor. In contrast, claims 1-7 of patent number 6,027,933 are directed to a kit for the preparation of vectors and do not recite vectors having any DNA sequences encoding polypeptides, much less a population of DNA sequences encoding polypeptides of a heteromeric receptor. Therefore, claims 16-25 and 26-33 do not claim the same invention as claims 1-7 of patent number 6,027,933.

Applicant respectfully submits that claims 68-75 of the application are also not directed to the same invention claimed in claims 1-7 of patent number 6,027,933. Specifically, claims 68-75 are directed to vectors having two copies of a gene encoding a filamentous bacteriophage. In contrast, claims 1-7 of patent number 6,027,933 are directed to a kit for the preparation of vectors and do not recite a vector having two copies of a gene encoding a filamentous bacteriophage. Therefore, claims 68-75 do not claim the same invention as claims 1-7 of patent number 6,027,933.

Accordingly, Applicant request that rejection of claims 16-32 and 68-75, under 35 U.S.C. § 101, be withdrawn.

Claims 1-5, 7 and 16-33 stand rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 1-8, 16-21 and 23-33 of application serial number 08/349,131, now claims 1-32 of U.S. Patent Number 5,871,974. In this regard, the Office Action alleges that the claims are not patentably distinct from each other because the claims in the instant application completely encompass the subject matter claimed in U.S. Patent Number 5,871,974.

Applicant respectfully traverses the rejection and contends that claims 1-5, 7 and 16-33 of the instant application are not obvious over claims 1-32 of U.S. Patent No. 5,871,974. Specifically, claims 1-5 and 7 are not obvious variants of claims 1-32 of U.S. Patent No. 5,871,974 because the plurality of cells recited in claims 1-5 and 7, are directed to the species procaryotic cells whereas the claims of the cited patent are directed to the genus cells. A genus does not, on its face, render obvious one of many particular species.

Moreover, in regard to the timeliness of filing a terminal disclaimer, Applicant respectfully submits that because the subject matter of the claims has not been resolved there is nothing concrete to disclaim. Applicant, therefore respectfully requests deferral of this issue and upon indication of allowable subject matter in the application, a terminal disclaimer, if appropriate, will be timely filed.

CONCLUSION

In light of the amendments and remarks herein, Applicants submit that the claims are now in condition for allowance and respectfully request a notice to this effect. Should the Examiner have any questions, he is invited to call the undersigned agent or Cathryn Campbell.

Respectfully submitted,

August 28, 2001
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Serial No.: 08/471,622
Filed: June 5, 1995

APPENDIX A

Marked up versions showing amendments made to the claims:

66. (Amended) A vector comprising two copies of a gene encoding a filamentous bacteriophage coat protein, one copy of said gene [capable of] being operationally linked to a DNA sequence encoding a polypeptide of a heteromeric receptor, [wherein] said DNA sequence being [can be] expressed as a polypeptide of a fusion protein comprising said heteromeric receptor on the surface of said filamentous bacteriophage or as a soluble polypeptide.

71. (Amended) A vector comprising sequences necessary for the coexpression of two or more inserted DNA sequences encoding polypeptides which form heteromeric receptors and two copies of a gene encoding a filamentous bacteriophage coat protein, one copy of said gene [capable of] being operationally linked to one of said two or more inserted DNA sequences, [wherein] said DNA sequence being [can be] expressed as a polypeptide of a fusion protein comprising said heteromeric receptor on the surface of said filamentous bacteriophage or as a soluble polypeptide.